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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/348,354	07/07/99	HAVENGA M	4123US

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EXAMINER	
BRUNOVSKIS,P	
ART UNIT	**PAPER NUMBER**
1632	17

DATE MAILED: 09/04/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Advisory Action

Application No.	Applicant(s)
09/348,354	Havenga et al.
Examiner	**Art Unit**
P ter Brunovskis	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED *Aug 16, 2001* FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.

b) ☐ In view of the early submission of the proposed reply (within two months as set forth in MPEP § 706.07 (f)), the period for reply expires on the mailing date of this Advisory Action, OR continues to run from the mailing date of the final rejection, whichever is later. In no event, however, will the statutory period for the reply expire later than SIX MONTHS from the mailing date of the final rejection.

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will be entered upon the timely submission of a Notice of Appeal and Appeal Brief with requisite fees.

3. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search. (See NOTE below);

   (b) ☐ they raise the issue of new matter. (See NOTE below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without cancelling a corresponding number of finally rejected claims.

   NOTE: _____

4. ☒ Applicant's reply has overcome the following rejection(s):
Indefiniteness over "adapted" in claim 2 (not claim 1); "tropism" and "plurality" in claims 1 and 2; "functional part" in claim 2. Claim 1 remains indefinite concerning "adapted" because the claim fails to make clear (see "Other" below)

5. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in separate, timely filed amendment cancelling the non-allowable claim(s).

6. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because:
Indefiniteness rejection over "adapted" in claim 1 is maintained for reasons of record, since "adapted" is not defined in the specification and since it remain unclear whether the chimeric adenovirus is structurally modified (see "Other"

7. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

8. ☒ For purposes of Appeal, the status of the claim(s) is as follows (see attached written explanation, if any):

   Claim(s) allowed: *none*

   Claim(s) objected to: *none*

   Claim(s) rejected: *1-3 and 9-11*

9. ☐ The proposed drawing correction filed on _____ a) ☐ has b) ☐ has not been approved by the Examiner.

10. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

11. ☒ Other: *(or genetically engineered) at both the fiber- AND penton/hexon levels or only one of the two. Prior art rejection maintained for reasons of record (see attached)*

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Attachment to Advisory Action

The response argues "that it is inappropriate to cite the inherency in Crystal of a 'particular tropism adapted for a particular plurality of target cells in a host' when Applicants have claimed fiber protein having desired tropism" (paragraph abridging p. 7-8). The response further asserts that "[i]n order for Crystal to anticipate this element of the claimed invention, it must either expressly or inherently describe fiber protein having desired tropism, not just a particular tropism. While it is true that in the entire universe of adenoviral fiber proteins, each different fiber protein will exhibit a particular tropism, it is not the case that all fiber proteins will exhibit a tropism that is desirable for a given application...[and that]...[t]his distinction is important to applicants' claimed invention and is not described in Crystal" (top of p. 8).

To the contrary, Crystal points out that recombinant adenoviral vectors (as in the disclosed invention) "are additionally preferred based on their normal tropism for the respiratory epithelium in cases where the targeted tissue for somatic gene therapy is the lung" (col. 1, lines 37-40). Since the adenoviral vectors disclosed contain a fiber "adapted" for such a tropism and since Crystal discloses variants in the fiber, coat, and/or penton base proteins responsible for tissue tropisms and/or immunogenicities, the disclosure of Crystal clearly anticipates the claimed subject matter of the instant invention. Inasmuch as Crystal implicitly teaches that adenoviral vectors of the disclosed invention have a desirable tropism for respiratory epithelium, Crystal meets the intended use limitation in the recited claims of the instant application.

The response concedes that "[i]n order for Crystal to anticipate this element of the claimed invention [i.e. desired tropism], it must either expressly *or inherently* described fiber protein having desired tropism, not just a particular tropism" (top of p. 8; emphasis added). As pointed out in the Office Action of 4/17/01 in accordance with MPEP 2112, "[o]nce a reference teaching product appearing to be substantially identical is made the basis of a rejection and the examiner presents evidence or reasoning tending to show inherency, the burden shifts to the applicant to show an obvious difference". However, the response fails in its burden to point out any *structural difference* between the claimed invention and the prior art, so as patentably distinguish the claimed invention from the prior art. The mere recitation of an intended use limitation does not provide for a structural difference between the claimed invention and the prior art, particularly in view of *Ex parte Obiaya*, which teaches that even if the prior art disclosure did not recite or recognize a property or advantage that would flow naturally from following the suggestion of the prior art, this observation cannot serve as the as the basis for patentability over the prior art when the structural differences are otherwise identical. The response failed to address this argument previously set forth in the Office Action of 4/17/01.

In agreement with Applicants position on p. 8, "[o]nce the Office has established a *prima facie* case for inherency, the burden shifts to the applicant to rebut inherency with evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product". Importantly, the response fails to rebut the prima facie evidence for inherency as directed to Crystal's disclosure of an adenoviral vector comprising a fiber protein comprising a

fiber protein from one adenovirus serotype, Ad5, and at least a part of a hexon protein from a second serotype, Ad7, wherein the second adenovirus serotype (i.e. Ad7) has lower relative tropism to a plurality of cells than the chimeric adenovirus (as specified by the Ad5 fiber protein) and wherein the second adenovirus serotype (Ad7) has less antigenicity than the first adenovirus serotype (i.e. Ad5) as evidenced by Applicants 1.132 declaration (see e.g. Figure 1) *and Table 2, p. 73 of the instant specification*, which clearly illustrates a difference in tropism between the two, depending on the type of tropism deemed "desirable". The *specifications'* teachings constitute adenoviral tissue tropism is germane to the question of inherency, not whether Crystal mentions such tropisms or whether Dr. Havenga's declaration makes any reference to tissue tropism as argued in the response (top of p. 9).

It is important to note that the rejected claims are not drawn to any particular "desired tropism"; rather, the recited claim limitation is merely a statement of intended use wherein the measure of "desirability" is highly subjective. What can be deemed desirable for one application would be undesirable for another. Given that modified fibers exhibit diverse patterns of tropism, it is not hard to envision multiple embodiments within the broad scope of Applicants claimed invention that would be anticipated by the disclosure of Crystal, particularly in view of Applicants own evidence concerning inherent tropisms and antigenicities of the various adenoviral serotypes.

Inherency, in the instant case is not based on probabilities or possibilities, but rather Applicants own evidence which substantiates Crysal's disclosure as anticipating the subject matter as claimed. Moreover, the fact that Applicants may have recognized certain characteristics

concerning specific adenoviral tropisms or antigenicities does not obviate the grounds for rejection under inherency, particularly when the invention is so broadly claimed as in the instant case. Determining whether a prior art disclosure anticipates the claimed *compositions* depends on evaluating whether a given composition meets the structural and functional limitations recited therein, independent of whether the disclosure itself reveals the distinction. The Office has met its burden in establishing a prima facie case for anticipation based on both a broad interpretation of the claims and evidence concerning inherency as set forth in the Office Action of 4/17/01 and as set forth herein.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Brunovskis whose telephone number is (703) 305-2471. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda can be reached at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Patent Analyst, Patsy Zimmerman whose telephone number is (703) 308-8338.

Peter Brunovskis, Ph.D.
Patent Examiner
Art Unit 1632